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October 26, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 99D-2635; Draft Guidance for Industry on
ANDA's: Blend Uniformity Analysis; Notice of
Availability and Request for Comments Appearing in
Federal Register of Friday, August 27, 1999
(64 FR 46917)

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier, and more productive lives. Investing \$24 billion a year in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA member firms are sponsors of new drug applications (NDA's), abbreviated new drug applications (ANDA's), supplemental applications thereto, and are subject to FDA regulations covering current good manufacturing practices (cGMP) for finished pharmaceuticals as set forth in 21 CFR parts 210 and 211. Since the proposed draft guidance is intended to provide recommendations to sponsors of ANDA's on "establishing in-process acceptance criteria related to blend uniformity analysis (BUA) for the manufacture of some drug products," as well as recommendations on when BUA should be performed, our members are vitally interested in the subject draft guidance and its implications for required documentation to be submitted in drug applications and for compliance with applicable cGMP's relating to in-process testing requirements.

PhRMA appreciates the effort of the Agency in developing this document. However, the guidance continues to reflect positions to which many in the industry have previously provided scientifically based objections. PhRMA continues to be very concerned about requesting the continued sampling of blends using technology that is known to have significant problems.

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PhRMA recommends that the Agency either withdraw, reconsider or modify the guidance set forth in this document for the following reasons:

1. It is not technically feasible at this time to consistently obtain representative blend samples of 1-3 times the dosage weight,
2. In-process blend testing is not required by regulations, nor is it needed,
3. Technical input from the Product Quality Research Institute (PQRI) should have been obtained prior to issuance of the draft guidance,
4. The proposed testing adds little value but results in substantial expense to pharmaceutical manufacturers,
5. The proposed acceptance criteria are without scientific merit,
6. The 50mg/50% requirement should be modified to provide consistency with the USP and ongoing pharmacopeial harmonization efforts, and
7. The proposed testing may present barriers to the introduction of, and application of beneficial industry technology.

Each of these identified issues is discussed below in our specific comments on the draft guidance. PhRMA believes that blend uniformity is more properly handled as a process/product validation issue. Initial validation of the drug manufacturing process, periodic revalidation studies, annual drug product quality reviews, and batch dose uniformity testing represent the current industry standard to assure batch uniformity. PhRMA is concerned that the draft guidance calls for unnecessary additional testing which would only increase the costs for drug manufacturing while offering no public health value. It is PhRMA's opinion that the draft is not sufficiently clear in its intended scope, causes a great deal of confusion regarding its applicability and, as drafted, does not adequately reflect the important differences between the review documentation necessary for drug applications and the compliance and field investigator responsibilities applicable to adherence to cGMP's.

More generally, PhRMA has concerns about the process within FDA for the development of this draft guidance and its issuance as intended only for ANDA's. In our view, it would have been more appropriate for a draft Agency guidance for this important topic to have had the benefit of discussion with the affected industry, full discussion among all of the relevant Center for Drug Evaluation and Research (CDER) Divisions and possible workshops or forums. Additionally, the Agency must be aware that the PQRI, as noted above, has identified BUA as one of its highest priorities for

investigation and research in the Drug Product Technical project area. Establishing draft guidance prior to obtaining the benefit of an impending scientific assessment seems to be in conflict with the Agency's announced commitment to the application of sound scientific principles in all of its regulatory policies. For all of these reasons PhRMA urges the Agency to withdraw or reconsider the subject draft guidance.

PhRMA has the following specific comments on the draft guidance:

1. It is not technically feasible at this time to consistently obtain representative blend samples of 1 – 3 times the dosage weight.

When a blend is sampled and assayed, there will primarily be three sources of variance. These are the inherent blend non-uniformity, assay variance, and sampling error¹. The first of these, blend non-uniformity, is the quantity that one is attempting to measure. The second, assay variation, is familiar to the FDA as well as the industry. Measures of its extent are usually obtained during method validation. The third is sampling error.

The difficulties in obtaining small samples using a sampling thief from a blender have been well established with a body of literature extending over several decades [1, 2 and additional references in reference section of these comments]. The sampling thief tends to segregate the material resulting in a sample that is not representative of the blend. The frequent consequence is assay results that have a significant bias and are highly variable.

In many instances, the sampling error will comprise a substantial part of the total measured variation, and may lead to a disproportionate number of batches being inappropriately rejected. Because thief sampling from a static powder bed should generally be avoided, capturing a 10X sample may not improve the situation.

In addition, the entire sample should be analyzed. To attempt to subdivide this sample to obtain a 1X sample for analysis may result in a segregated sub-sample. Experience has shown that the sub-sample results may not be representative of the original sample. Results have been seen that are biased and have shown high variability as one tries to sub-divide the original samples in the laboratory.

Industries that manufacture powders have long been concerned with powder sampling. A well-known text on this subject is that authored by Allen [3]. He describes two golden rules of powder sampling:

¹ As these variance sources are independent, the total variance is the sum of the three components. (Weight variation is not included as blend assay results are usually normalized to the unit dose weight.) The standard deviation is the square root of the total variance.

1. A powder should be sampled when in motion.
2. The whole of the stream of powder should be taken for many short increments of time in preference to part of the stream being taken for the whole of the time.

Allen describes a number of acceptable ways of first capturing a bulk sample while the powder is in motion. He advocates obtaining an appropriately sized subsample for analysis by using a spinning riffler. However, he cautions this works best only if the powder is free flowing. Allen concludes his section on the sampling of powders with a thief by stating:

“The accuracy (or inaccuracy) of the sampling spear is comparable to the accuracy of scoop sampling and, on the whole, is to be deprecated [4].”

Clearly, requiring that small samples of 1 – 3 times the dosage weight be withdrawn from powder beds many orders of magnitude larger as an in-process test during routine manufacture is not an acceptable practice. Alternatives must be found that will satisfy the Agency's concerns.

2. In-process blend testing is not required by the CFR nor is it needed.

The guidance states that the in-process testing requirement for adequacy of mixing to ensure homogeneity and uniformity is established in 21 CFR 211.110(a)(3). However, in-process controls do not necessarily have to measure the critical parameter in question. For example, this section of the cGMP's also states that in-process testing should control for dissolution time and rate. Obviously, for an uncoated tablet or a capsule, one tests this parameter as part of release testing. However, frequently the moisture content of a blend or the hardness of a tablet are monitored because of known relationships between these parameters and dissolution rate. On the other hand, if such relationships do not exist, the manufacturer relies upon a validated, well-developed process to ensure a product with consistent and appropriate dissolution properties. In this case, in-process tests are not performed, nor are they necessary. Although this guidance is promulgated as an in-process requirement, in reality it is an additional release requirement. As such, it is not adhering to the stated purpose of 21 CFR 211.110(a)(3).

Modern blending operations have been well developed and validated. Requirements are frequently imposed on the particle size distributions of active ingredients and excipients to ensure adequacy of mixing. Blender operations, including the addition sequence of the ingredients, are optimized. Industry reports have been issued suggesting appropriate procedures for conducting blender validation [6]. Therefore,

credible evidence has been documented providing assurance that the blending operation is producing a powder that is consistently able to meet the content uniformity requirements of the submission. This is substantiated by content uniformity release testing during routine manufacture. Thus, the current CFR requirements assure content uniformity, and a new requirement for in-process blend testing is not necessary.

3. Technical input from the PQRI was not provided prior to issuance of the draft guidance.

The BUA draft guidance states that the Agency intends to seek the support of the Product Quality Research Institute on blend uniformity issues. PhRMA commends this objective, but, would not a more prudent course of action be to obtain technical, scientific and research support before issuing a guidance?

4. The proposed testing adds little value but substantial expense.

This guidance will impose significant expense on the manufacture of pharmaceutical products. These costs will come from three activities:

1. Added analytical expense,
2. Added investigative resources required by QA groups, and
3. Loss in yield

The third expense may be particularly significant. Exhibit 1 indicates the results of a simulation to determine the operating characteristic curves of the proposed acceptance criteria. For example, the simulation results indicate that a blend with a process standard deviation of 4% (which includes sampling error) will fail the acceptance criteria about 16% of the time. (A tablet with the same process standard deviation and assay mean (100%) will consistently pass the USP content uniformity test.) The percent of batches failing rises to 40% with a process standard deviation of 5%, and is even larger if the process mean is different than 100%. As this material will not generally be eligible for rework, the sampling and testing requirement will result in an overall loss in yield for the product. Yet, because of the issues previously raised, the blend data that is obtained from this exercise will generally be of little value.

5. The proposed acceptance criteria have little scientific merit.

The draft guidance recommends acceptance criteria requiring that the RSD of six samples be less than 5.0%, and that the mean be between 90.0% - 110.0%. These criteria have little scientific merit. This conclusion is based upon the following:

- The criteria are not related to the susceptibility of a specific blend to segregate.

There is no one standard that can be set at the blend stage that will provide assurance that the product will meet uniformity requirements. Every blend is unique. Some blends will have a tendency to segregate, and hence must be more homogeneous at the blender stage to provide adequate uniformity in the final product. Other blends do not share this tendency. In fact, some blends may remix during processing.

The only way to provide a universal acceptance criterion at the blender stage is to have a very stringent criterion. However, this would unnecessarily penalize the large majority of products that do not demonstrate a propensity for undue segregation. With a very stringent criterion, many products would unnecessarily fail because of thief sampling error.

- There is no provision to adjust the criteria, in a statistically consistent manner, for sample sizes larger than 6.

If one chooses to use a larger sample size than six, provision should be made for a less stringent criterion for the RSD. The alternative criterion should be statistically consistent with the currently proposed criterion, i.e., provide the same level of confidence that the true process RSD meets an agreed standard.

- To impose a criterion on the mean of blend samples is inconsistent with the objective of measuring blend homogeneity.

Variability is measured by such appropriate statistics as RSD and standard deviation. The potency of a product is properly measured at the final product stage. Further, sampling error will frequently express itself as a bias in one particular direction. For example, all assays may be significantly less than 100%. Examples can be cited in which the mean of blend assays approached 90%, yet the mean of the product was approximately 100%. Imposing a criterion on the mean of the blend samples increases the probability of erroneous failures.

- There is no valid reason not to have a two-tier test.

This requirement is too restrictive. The USP content uniformity test is a two-tier test. Further, because of the possibility of thief sampling error, the most logical course of action to take if the blend samples do not meet their acceptance criteria is to investigate the possibility of poor product homogeneity by extensive testing of the product. The relevant literature contains many examples where firms experience questionable BUA results while the corresponding content uniformity data are well within limits.

Results from a simulation to develop the operating characteristic curves for the proposed acceptance criteria may be found in Exhibit 1.

6. The 50mg/50% requirement should be modified to provide consistency with the USP.

While the current version of the USP allows content uniformity by weight variation when the active ingredient is greater than 50 milligrams and greater than 50 percent of the dosage form unit by weight², this might not always be the case. PhRMA agrees with the FDA that chemical testing for blend uniformity should not be performed if chemical testing is not required for product content uniformity. However, a proposal under current consideration as part of the ICH Q6A guidance for "Setting Drug Substance and Drug Product Specifications" and its related pharmacopeial harmonization effort has recommended that this demarcation be changed to greater than 25 milligrams and greater than 25 percent. In the future, the USP may adopt this proposal. In following the original logic of the FDA, it would seem that blend uniformity analysis should be required of only those products requiring chemical testing for content uniformity. This flexibility should be built into the guidance at this time.

7. The requirement may interfere with beneficial industry trends.

Aside from the above technical considerations, there are

² Note – the draft guidance incorrectly states:

"If the composition of the drug product is greater than or equal to 50 milligrams of the active ingredient per dosage form unit or the active ingredient is greater than or equal to 50 percent of the dosage form unit by weight, blend uniformity analysis is not usually necessary."

The underlined "or" in the above quote should be replaced with an "and."

important industry trends that need to be considered:

- Products are being developed that have more potent active ingredients, and therefore lower dosage strengths. The lower the dosage strength, the more difficult it is to obtain a uniform sample from the blend using a sampling thief. Low potency drugs, e.g., active of less than 1 mg, will often require a sample size for assay that is many times the equivalent of a single tablet weight. Compounding this problem is the trend toward direct compression formulas where particle size differences between active ingredient and excipients increase the likelihood of thief sampling error.
- In order to improve product quality as well as to comply with ever-tightening occupational health regulations, new processes are being developed in In-Bin blenders. After loading, the blending vessel remains sealed until it is emptied by discharging to a tablet press or encapsulator. Opening the vessel to remove a sample unnecessarily exposes the batch to contamination from the sampling thief, the operator, or the surrounding room. In-bin blending rooms are designed to not be cleaned between products since the blender is not supposed to be opened in the room. Opening the blender also potentially exposes the operator to a potent compound.
- This proposal cuts off new technology options. When available, technology such as Near Infrared (NIR) spectroscopy could be used to demonstrate intra-batch uniformity of mixing of all formulation ingredients. Although it does not demonstrate uniformity of potency, this should not be a concern since if the blend is uniform, the assay of the batch will provide the potency.

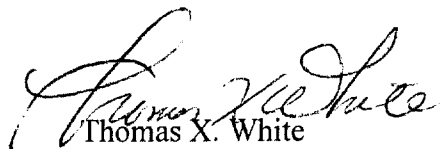
Conclusions

PhRMA understands that the effort required to generate this draft guidance may reflect agency concerns about industry practices. PhRMA is interested in obtaining a better understanding of these concerns. A clear indication by the Agency of their issues with blend uniformity will allow industry and the Agency to develop solutions that will be more scientifically sound and practical than the current draft guidance.

Blend uniformity testing is the top research project identified for the Drug Product Technical Committee within the PQRI initiative. PhRMA would support a forum for open discussion of the issue to better understand the concerns of the agency and to jointly develop alternatives to the draft ANDA BUA guidance.

Accordingly, PhRMA believes that issuance of a BUA guidance at this time is premature and urges FDA to either withdraw or modify it. PhRMA would welcome an opportunity to discuss any aspect of this issue with FDA.

Sincerely,



Thomas X. White

Enclosures: References
Exhibit 1

References

- [1] PDA Technical Report No. 25, *PDA Journal of Science and Technology*, Vol 51, Number S3, 1997, pp. S9 – S10.
- [2] Allen, T., *Particle Size Measurement*, 4th Ed., Chapman and Hall, New York, NY, 1990, p. 40.
- [3] Allen, T., *op cit.*, pp. 1 - 40.
- [4] Allen, T., *op cit.*, p. 18.
- [5] Muzzio, F.J., Robinson, P., Wightman, C., and Boone, D., "Sampling Practices in Powder Blending", *International Journal of Pharmaceutics*, 155 (1997) pp.153-178.
- [6] PDA Technical Report No. 25, *PDA Journal of Science and Technology*, Vol 51, Number S3, 1997, pp. S13 – S37.

Other References

- 1. Prescott, J.K., and Hossfeld, R.J., "Maintaining Product Uniformity and Uninterrupted Flow to Direct-Compression Tableting Presses," *Pharmaceutical Technology*, 18 (6), 98-114, 1994.
- 2. Chowhan, Z.T., "Sampling of Particulate Systems," *Pharmaceutical Technology*, 18 (4), 48-56, 1994.
- 3. Carstenson, J.T., and Dali, M.V., "Blending Validation and Content Uniformity of Low-Content, Noncohesive Powder Blends," *Drug Development and Industrial Pharmacy*, 22 (4), 285-290, 1996.
- 4. Berman, J., and Planchard, J.A., "Blend Uniformity and Unit Dose Sampling," *Drug Development and Industrial Pharmacy*, 21 (11), 1257-1283, 1995.
- 5. Garcia, T., Elsheimer, B., and Tarczynski, F., "Examination of Components of Variance for a Production Scale, Low Dose Powder Blend and Resulting Tablets," *Drug Development and Industrial Pharmacy*, 21 (18), 2035-2045, 1995.
- 6. Muzzio, F.J., Roddy, M., Brone, D., Alexander, A.W., and Sudah, O., "An Improved Powder-Sampling Tool," *Pharmaceutical Technology*, (4) 92-110, 1999.

Exhibit 1

Statistical evaluation of the proposed acceptance criteria in Section IV.

A simulation was performed using SAS to evaluate the proportion of batches that will fail the proposed criteria, given different standard deviations. The simulation assumes that the BUA samples have a true process mean as indicated below and that 6 samples are obtained from the blend using a thief.

The total standard deviation will includes assay, homogeneity, and sampling error. Thus the variability attributed to lack of homogeneity is smaller than the standard deviations in the table of results.

RESULTS: given a total standard deviation (including sampling and assay error), what is the percent of batches that will fail the criteria?

Acceptance Criteria Characteristic Operating Curves Percent of Batches not meeting criteria			
	True Process Mean, % of Label		
True Process Standard Deviation, %	100	96	92
3.0	2	2	8
3.5	7	9	18
4.0	16	20	32
4.5	28	32	45
5.0	40	45	57
5.5	52	57	67
6.0	62	66	75
7.0	76	79	85
8.0	85	87	91
9.0	90	92	94
10.0	94	95	96
12.0	97	98	98
14.0	99	99	99

For example, if the process standard deviation (including sampling and assay error) for a product is truly 5.0%, 40% of all batches with a process mean of 100% will fail BUA when 6 results are obtained and compared to the proposed criteria. However, even when a typical tablet weight variation is added to the other sources of variation, this batch should pass the USP Content Uniformity test with high confidence. Therefore, this means that 4 in 10 batches with acceptable levels of variation will be rejected during the blending evaluation.